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Nitrofurantoin in Treatment of Coliform Bacteremia

Report of a Case

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THE USE OF FURADANTIN® (nitrofurantoin, N. N. R.), one of the group of antibacterial nitrofurans, has been established in the treatment of resistant strains of certain gram-positive and gram-negative bacterial infections of the urinary tract. The general literature was reviewed by Trafton and co-workers⁹ but the treatment of bacteremia was not included. In a medical research forum at the New York Academy of Medicine, Friedgood and Ripstein² briefly mentioned six cases of *B. proteus* septicemia successfully treated with Furadantin but gave no details.

Consequently, reports to date do not deal with bacteremia but rather with infections limited to the urinary tract. The purpose of the present communication is to report in detail the successful treatment of a case of persistent bacteremia due to *E. coli*, the focus of which was presumably the urinary tract, and to discuss the possible relationship of the disease in this case to the administration of adrenocortical hormones. In this particular case, bacteremia was not cleared by administration of streptomycin in combination with certain of the broad spectrum antibiotics.

CASE REPORT

A 63-year old man had sudden onset of a shaking chill and fever, followed shortly by nausea, vomiting and prostration. Chills continued, prostration increased and the patient was admitted to hospital at night, six hours after the onset of symptoms. The patient had had mild dysuria and low backache for two days before the acute illness developed. Upon physical examination the patient was observed to be prostrated and the skin was flushed and dry. The temperature was 101° F., the pulse rate 104 and blood pressure 140/75 mm. of mercury. Severe shaking chills continued and at 1 o'clock in the morning, following an unusually heavy chill, the

temperature was 107° F. (This temperature was confirmed.) At that time a specimen of blood was obtained for culture, and 600,000 units of aqueous procaine penicillin then was administered intramuscularly.

The following morning, the temperature was 103.2° F., the pulse rate 112 and blood pressure 74/50 mm. of mercury. The patient was lethargic but could be aroused. The skin was flushed and dry but without eruption or petechiae. Pulses were equal, rapid and regular. Heart sounds were somewhat distant but there were no murmurs. The lungs were clear. The abdomen was flat and no masses were palpated. Slight tenderness was noted in the right upper quadrant.

The urine was turbid with acid reaction, specific gravity of 1.018, a 1 plus reaction for albumin and a trace of sugar. Acetone and diacetic reactions were negative. Upon microscopic examination of centrifuged sediment, a solid field of erythrocytes and 10 to 15 leukocytes per high power field were noted. A few gram-negative rods were seen. There was a heavy growth of *E. coli* on a culture of the urine.

Erythrocytes numbered 4,250,000 per cu. mm. and the hemoglobin content was 13.2 gm. per 100 cc. Leukocytes numbered 7,650 per cu. mm.—40 per cent stab neutrophils, 42 per cent adult neutrophils, 7 per cent lymphocytes, and 1 per cent monocytes. There was pronounced toxic granulation of the neutrophils.

In view of the urinary abnormalities and the relative leukopenia with a pronounced shift to the left, it appeared clear that the patient had bacteremia from a focus probably in the urinary tract. Accordingly, 500 mg. of chlortetracycline was administered intravenously without delay and a similar dose was given six hours later. The hypotension and obvious apathy suggested the possibility of impending shock, perhaps due to adrenal cortical damage, and 40 cc. of adrenal cortical extract was given intravenously over an 8-hour period. Cortisone was begun in a dosage of 200 mg. daily, given by mouth at 6-hour intervals.

Early in the afternoon of the day following admittance, a report was received that gram-negative bacilli grew on a culture of blood. A combination of oxytetracycline and streptomycin was begun in total daily doses of 1.5 gm. and 4.0 gm. respectively, the latter intramuscularly.

While arrangements were being made for the administration of adrenal cortical extract, the blood pressure decreased to 68/50 mm. of mercury. After the administration of 10 cc. of adrenal cortical extract, the pressure rose to 82/50 mm. and by the time of administration of the second 10 cc. dose one hour later, it was 98/56 mm.

Data on the subsequent course are given in Chart 1. Daily blood cultures were obtained, the blood pressure was carefully observed, and leukocyte and differential counts were made daily. The blood pressure rose to 130/78 mm. of mercury the day

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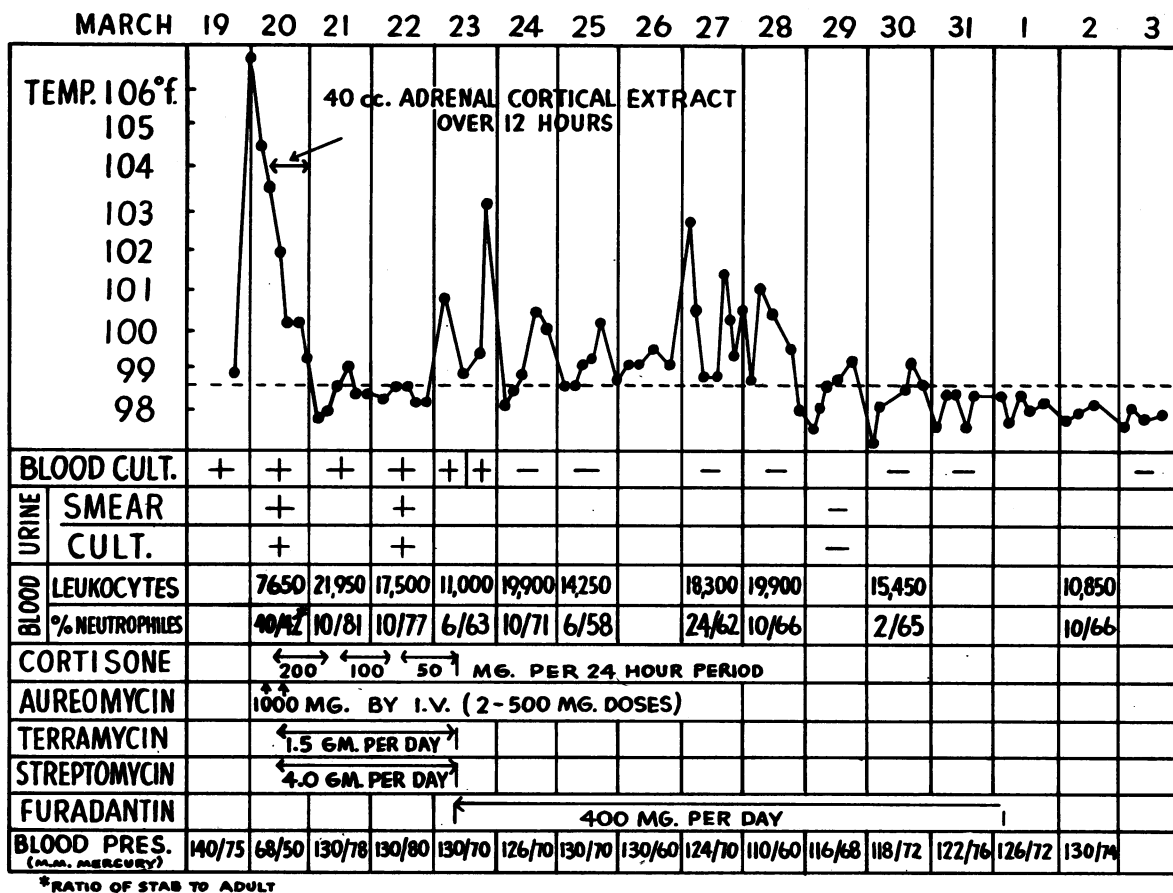


Chart 1. Clinical, laboratory and therapeutic data on a case of *E. coli* bacteremia successfully treated with Furadantin (nitrofurantoin) after unsuccessful use of streptomycin, chlortetracycline (Aureomycin), and oxytetracycline (Terramycin). Note that initiation of Furadantin coincides with cessation of cortisone administration.

after administration of adrenocortical hormones was begun and thereafter did not significantly change (Chart 1). Bacteremia continued—one or two colonies per cc. of blood on the culture. The leukocyte content rapidly rose and the shift to the left decreased. Twenty-four hours after the administration of cortisone was begun, the dosage was reduced to 100 mg. daily, and on the third day to 50 mg. daily. The patient's clinical appearance improved but on the fourth day in the hospital the temperature began to rise even though albumin had disappeared from the urine and only scattered erythrocytes and a few leukocytes were seen in microscopic examination of the sediment. Repeated physical examinations were carried out but a specific focus of infection in the urinary or gastrointestinal tracts could not be identified. No heart murmurs were heard.

With the temperature rise to 100.8° F. on the fourth day and the fact that bacteremia was still present as of the preceding day (Chart 1) a second culture of blood (which subsequently proved to be positive) was made and treatment was changed abruptly. Oxytetracycline and streptomycin were discontinued and Furadantin was administered by

mouth, 100 mg. every six hours. Cortisone was also discontinued at the same time.

Following this change in therapy, all blood cultures were sterile and the temperature gradually decreased. On the eighth hospital day the leukocyte content of the blood increased and young forms of neutrophils reappeared. Upon physical examination the left testicle was observed to be enlarged, reddened and very tender. A urological consultant attributed these symptoms to acute epididymitis. Appropriate local treatment led to a regression of the lesion and favorable changes in the leukocyte content and differential.

Cystopyelographic examination was carried out on the tenth hospital day. The anterior urethra was normal. There was slight enlargement of both lateral lobes of the prostate but no enlargement of the middle lobe. Generalized contracture of the neck of the bladder was noted. Sphincter tone was good. The bladder wall showed many coarse trabeculations and openings of three small diverticula were noted. Both ureteral orifices were normal in size, position and appearance. Retrograde pyelograms were made, and no abnormality was observed in the upper urinary tracts, but there was an incompletely filled diver-

ticulum about 3 cm. in greatest diameter extending laterally from the left side of the base of the bladder. A single smaller diverticulum about 1 cm. in diameter was observed at the left side of the fundus. A film made with the patient upright, following withdrawal of the catheters, showed satisfactory drainage of both upper urinary tracts and normal mobility of both kidneys.

In view of the presence of diverticula, catheter drainage of the bladder was begun and was continued throughout the remaining period of hospitalization.

Further roentgenographic studies revealed pulmonary emphysema with old pleuritis of the left base, atherosclerosis of the aorta and (after a double dose of Telepaque®) poorly functioning gallbladder. No abnormality was observed in films of the colon.

Furadantin was discontinued after it had been given nine days with a dosage of 400 mg. daily. Nonprotein-nitrogen content was 28.6 mg. per 100 cc. of blood the day before Furadantin therapy was started. After five days it was 43.0 mg., and at the end of nine days 44.0 mg. per 100 cc. The day following discontinuance of Furadantin it was 39.2 mg. The patient continued to improve and was discharged 14 days after admittance. There was no recurrence of symptoms up to one year after discharge.

Results of disc sensitivity tests carried out on the organism isolated from the first culture of blood were reported by the Peralta Hospital laboratory as follows: Resistant to penicillin, erythromycin, chloramphenicol, chlortetracycline and oxytetracycline; moderately sensitive to streptomycin; highly sensitive to Furadantin. Studies on the same organism carried out in the Bacteriology Laboratory of Stanford University Hospital by the plate-screening method of Rantz⁷ revealed the following: Resistant to penicillin, polymixin, erythromycin and bacitracin; sensitive to streptomycin, oxytetracycline-chlortetracycline, chloramphenicol and neomycin. Identification of the organism as *E. coli* was confirmed.

DISCUSSION

The portal of entry of the infecting organism was doubtless the urinary tract, probably the bladder diverticula, in which there was mild cystitis. At no time during the course of the illness was there any evidence of acute prostatitis or prostatic abscess. Epididymitis may have occurred only as a complicating factor during convalescence. Likewise there was no evidence of significant abnormality of the gastrointestinal tract.

The success obtained with Furadantin in clearing the bacteremia is quite clear, since blood cultures taken up to and through the afternoon of the day Furadantin therapy was begun were positive. Within 18 hours after administration of Furadantin, the blood culture became sterile, as did subsequent cultures. (Cortisone was discontinued at the same time, a factor to be taken up later in this discussion.) It is likewise evident that streptomycin, chlortetra-

cycline, and oxytetracycline failed to clear the blood stream, although there was an apparent clinical improvement for several days after these agents were used. The combination of streptomycin and oxytetracycline cannot be considered to be an antagonistic combination, since the simultaneous use of streptomycin and tetracyclines is recognized as clinically proper for the treatment of resistant infections due to certain gram-negative bacilli⁸ and, in some instances, not theoretically improper.⁴

The mechanism of clearing the blood stream is of interest, since in this case the focus of infection was probably cleared by Furadantin with a resultant cessation of further seeding of the blood stream. It is reasonable to suppose that the concentration of Furadantin in the blood stream was not sufficient to act directly upon circulating organisms as do other generally more bactericidally potent agents.

The discrepancy between the two methods—the commercial disc method and the plate-screening method—of sensitivity testing for the strain of *E. coli* is worthy of note and points up the fact that these *in vitro* tests do not necessarily always parallel clinical response. They must be looked upon as useful in the way of general guidance but should never supplement clinical judgment and careful clinical observations made during the course of therapy.

The shock-like syndrome observed in this patient, with evidence of pronounced hypotension and apathy, is occasionally seen in cases of severe and overwhelming bacteremia. Whether, in the present patient, this was due to peripheral vascular collapse presumably due to bacterial toxins,¹ or to adrenal cortical damage as classically demonstrated in the Waterhouse-Friderichsen syndrome, or to some unknown kind of inhibition of the adrenal cortex, is not clear. Certainly, the use of adrenal cortical extract promptly raised the blood pressure, which then continued at a satisfactory level with the follow-up administration of cortisone. A similarly beneficial response was observed by the author in another case of overwhelming bacteremia with *E. coli*, treated in the same manner, in which the patient's condition was critical prior to adrenocortical hormone and antibiotic therapy.

The fact that two changes were made in treatment at the time bacteremia was cleared—namely, the institution of Furadantin by mouth and the discontinuing of cortisone—raises a question. While it seems clear that the use of Furadantin was the principal and important change, the possibility that cortisone may have played a role in the failure of the broad spectrum antibiotics must be considered. It is well known that the use of adrenocortical hormones may lead to the development of high levels of bacteremia⁶; however, it is likewise clinically known that the use of appropriate antibiotic agents will prevent such complications. Furthermore, Germuth, Ottinger, and Oyama³ have brought out the fact that such increased bacteremia is due not to a result of interference with the clearing mechanism but rather to the enhanced multiplication or entry from the infected tissues.

Jawetz⁵ has gone one step further and has studied the effect of Cortisone on the therapeutic efficacy of antibiotics in experimental infections. His data show that cortisone may interfere with the therapeutic effectiveness of antibiotics, the magnitude of the effect depending upon the severity of infection and the dosage of the antibiotic. However, in his studies the reduction of the therapeutic effectiveness of the antibiotic by cortisone was not evident when the antibiotic agent was given in large excess beyond the curative dose. Consequently, it is clear that cortisone usually plays little role in clinical medicine if the dosage of the antimicrobial agent is well in excess of the minimal curative dose.

Unless the strain of *E. coli* in the present case was an organism unusually resistant to the certain broad spectrum antibiotics employed, the therapeutic superiority of Furadantin in this case is supported.

SUMMARY

Bacteremia due to *E. coli* disappeared with the administration of Furadantin after failure with streptomycin, chlortetracycline, and oxytetracycline therapy. It was considered that Furadantin did not clear the blood stream *per se*, but rather cleared the focus of infection.

A shock-like syndrome due to the bacteremia was controlled by the use of adrenal cortical extract and cortisone. The possible inhibitory effects of the adrenocortical hormones on the broad spectrum antibiotics is discussed, and it should be pointed out that improvement coincided with the simultaneous cessation of their use and the administration of Furadantin.

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Presumptive Herpes Zoster Meningoencephalitis

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HERPES MENINGITIS in the differential diagnosis of poliomyelitis is unusual. That is why the following case is being reported. During a busy admitting night at the Communicable Disease Unit of the Los Angeles County General Hospital many patients are admitted with a diagnosis of acute anterior poliomyelitis, then are found to have an entirely different and unsuspected disease. Several of the more common are various types of bacterial meningitis, mumps meningoencephalitis, influenza syndrome and, more rarely, spinal coccidioidomycosis, infectious neuronitis or Guillain-Barré syndrome, and brain or cord tumor.

It is not generally known that the herpes zoster virus can also cause symptoms similar to those of acute poliomyelitis. In 1947 McCormack¹ reported a case in a four-year-old girl with complete recovery. Nachman² added three more cases to the pediatric literature in 1951. In those cases also there was complete recovery. Terterka and co-workers³ reported 44 cases of paralysis accompanying herpes in adults and only seven of the patients recovered completely. The benign course of the disease in a 19-year-old girl, the subject of this report, coincided with the course of the disease reported in the pediatric literature.

REPORT OF A CASE

A 19-year-old girl of Jewish parentage was admitted with complaint of dull prefrontal headache for five days. When pain in the neck, stiffness of the back and nausea developed, she was referred to the Communicable Disease Hospital with suspicion of poliomyelitis. On physical examination she appeared acutely but not severely ill. The temperature was 99° F., the pulse rate 74, respirations 20 per minute and blood pressure 120/80 mm. of mercury. The skin was clear except for one tiny vesicle on an erythematous base on the left flank. No abnormalities were observed in the head, eyes, ears, or throat. The neck and back were moderately stiff. The chest was clear. The heart was normal. The abdomen was soft and there were no palpable abnormalities. Hamstring spasm was not present.

On neurological examination there were no bulbar signs or reflex changes. No muscular weakness was noted.

Results of examination of the blood and urine were within normal limits. The cerebrospinal fluid was ground glass in appearance; and on microscopic examination showed 339 cells per high power field—95 per cent lymphocytes. The spinal fluid pressure was 170 mm. of water and the fluid flowed freely. The Pandy test reaction was 1 plus, and the sugar content normal.

From the Service of Dr. A. G. Bower, Chief Physician, Communicable Disease Unit, Los Angeles County General Hospital.